**Psychotropic medications and the risk of fracture: a meta-analysis**

Takkouche B, Montes-Martinez A, Gill S S, Etminan M

---

**CRD summary**

The authors concluded that psychotropic medications may moderately increase the risk of fractures, although the evidence may have been weakened by lack of accounting for important variables, and that further research is required. The authors’ cautious conclusion appears appropriate in view of the limitations of the data.

**Authors’ objectives**

To evaluate the risk of fracture in users of psychotropic drugs.

**Searching**

MEDLINE, EMBASE, LILACS and abstracts from meetings on the ISI Proceedings database were searched from database inception to December 2005 without any language restrictions; the search terms were reported. In addition, reference lists of retrieved articles and recent reviews and monographs were screened. Unpublished studies were not eligible.

**Study selection**

**Study designs of evaluations included in the review**

Case-control and cohort studies that provided either the relative risk (RR) of fracture and confidence intervals (CIs) or sufficient data to permit their calculation were eligible for inclusion. Cross-sectional studies were excluded. The included case-control studies used hospital- or population-based control patients.

**Specific interventions included in the review**

Studies of exposure to the following psychotropic medications were eligible for inclusion: benzodiazepines, antidepressants, antiepileptic drugs, antipsychotics, hypnotics and opioids.

**Participants included in the review**

Inclusion criteria for the participants were not specified. The participants in the primary studies included elderly patients, community-dwellers, women, white women, black patients with cerebral palsy, adults, patients with inflammatory bowel disease and patients of any age.

**Outcomes assessed in the review**

Studies that clearly reported fractures were eligible for inclusion. Studies reporting falls not followed by fractures were excluded. Most of the included studies assessed hip fractures; the types of fracture assessed by other studies were femur, femoral neck, vertebrae, long bones, appendicular, non-hip, non-spine, foot and any site.

**How were decisions on the relevance of primary studies made?**

Two reviewers independently conducted the searches. Any differences of opinion were settled by consensus.

**Assessment of study quality**

The authors did not state how the validity assessment was performed. A 10-point scale was developed for the needs of the review. The studies were assessed for: a participation rate of at least 80% for both treatment groups; cases incident or prevalent; source of controls (hospital or general population); adjustment or matching for potential confounding by age, gender, and cognitive and physical impairment; and accurate representation of duration of exposure to medication. In addition, cohort studies were assessed for loss to follow-up of less than 20% of the initial cohort and efforts made to assure that there were no sizeable changes in the exposure of the cohort during follow-up. Studies that scored at least 7 points were considered to be of a high quality.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, the measure of association between 'ever use' compared with 'never use' of psychotropic medication and the risk of fracture was extracted. For studies with more than one control group, the average relative risk (RR) was used.

Methods of synthesis
How were the studies combined?
The studies were grouped by type of antipsychotic drug. Adjusted odds ratios (ORs) for case-control studies and log RR for cohort studies were weighted by the inverse of their variance and combined using a fixed-effect or random-effects meta-analysis to give a pooled RR estimate with 95% confidence intervals (CIs). The random-effects model was selected when statistical heterogeneity was present. Publication bias was investigated using funnel plots and Egger's asymmetry test.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the DerSimonian and Laird Q test. In addition, the proportion of total variance due to between-study variance was calculated (Ri statistic). Subgroup analysis was used to examine the following potential sources of heterogeneity: study design, type of control, duration of exposure, study quality, type of fracture and class of drug. Where there was evidence of publication bias, a sensitivity analysis was performed by recalculating the RR using three specified assumptions.

Results of the review
The authors stated that they included 98 studies published in 46 reports. Thirty-five case-control studies (n approximately 1,000,000) and 11 cohort studies (n=278,806) were listed in the data extraction tables.

Benzodiazepines (23 studies: 16 case-control studies and 7 cohort studies).
Benzodiazepine use was associated with a significantly increased risk of fractures; the RR based on a random-effects model was 1.34 (95% CI: 1.24, 1.45). Statistically significant heterogeneity was detected (p=0.00001). Study design, type of control, duration of exposure and study quality did not appear to influence the RRs. There was no significant heterogeneity when the studies were grouped by duration of exposure. There was no evidence of publication bias from either the funnel plot or Egger's test (p=0.187).

Antidepressants (16 studies: 13 case-control studies and 3 cohort studies). Antidepressant use was associated with a significantly increased risk of fractures; the RR based on a random-effects model was 1.60 (95% CI: 1.38, 1.86). For cohort studies, the RR was lower and studies were statistically homogeneous (p=0.79). Case-control studies showed significant heterogeneity. Study quality did not appear to influence the RR. There was evidence of publication bias from the asymmetrical funnel plot and Egger's test (p=0.027).

Antiepileptic drugs (18 studies: 13 case-control studies and 5 cohort studies). Barbiturate use (5 studies) was associated with higher risks of fracture than non-barbiturate antiepileptic drugs (13 studies); the RRs were 2.17 (95% CI: 1.35, 3.50) and 1.54 (95% CI: 1.24, 1.93), respectively. Statistically significant heterogeneity was detected for both meta-analyses (p=0.00001 and p=0.007, respectively). Among studies of non-barbiturate antiepileptics, high-quality studies showed a more modest fracture risk than low-quality studies. For both drug classes, there was significant heterogeneity among case-control studies. There was evidence of publication bias from the asymmetrical funnel plot and Egger's test (p=0.025).

Antipsychotic (12 studies: 10 case-control studies and 2 cohort studies).
Antipsychotic use was associated with a significantly increased risk of fractures; the RR was 1.59 (95% CI: 1.27, 1.98). Statistically significant heterogeneity was detected (p=0.00001). Cohort studies were statistically homogeneous (p=0.42) but showed no significant difference in the risk of fracture between users and non-users. Case-control studies showed significant heterogeneity. Study quality, type of control and fracture site did not appear to influence the RR. There was evidence of borderline publication bias from the funnel plot and Egger's test (p=0.042).
Hypnotics (13 studies: 10 case-control studies and 3 cohort studies).

There was no significant difference in the risk of fractures between 'ever' and 'never' users of hypnotic drugs; the RR was 1.15 (95% CI: 0.94, 1.39). Statistically significant heterogeneity was detected (p=0.00001). Hospital-based case-control studies were statistically homogeneous (p=0.84) and showed a significant association between the risk of fractures and use of hypnotics (RR 1.53, 95% CI: 1.45, 1.61), although population-based studies did not. There was evidence of publication bias from the asymmetrical funnel plot and Egger's test (p=0.001).

Opioids (6 studies: 3 case-control studies and 3 cohort studies). Opioid use was associated with a significantly increased risk of fracture; the RR was 1.38 (95% CI: 1.15, 1.66). Statistically significant heterogeneity was detected (p=0.004). Cohort studies were statistically homogeneous but case-control studies were not.

Unspecified psychotropic drugs (10 studies). The use of unspecified psychotropic drugs was associated with a significantly increased risk of fracture (RR 1.48, 95% CI: 1.41, 1.59), with no significant heterogeneity (p=0.08) and no evidence of publication bias.

**Authors' conclusions**

Psychotropic medications may moderately increase the risk of fractures, although the evidence may have been weakened by confounding. Further research is required.

**CRD commentary**

The review addressed a clear question that was defined in terms of the intervention, outcomes and study design; inclusion criteria for the participants were not specified, which seemed appropriate given the area of the review. Several relevant sources were searched and attempts were made to minimise language bias. Although unpublished studies were not sought, the likelihood and potential impact of publication bias were investigated in the review. The quality of the included studies was assessed using specified criteria and sensitivity analyses were performed to assess the impact of study quality on the pooled results. The studies were combined in meta-analyses, statistical heterogeneity was assessed, and potential sources of heterogeneity were explored. The authors' cautious conclusion appears appropriate in view of the limitations of the types of studies included in the review and the potential for publication bias.

**Implications of the review for practice and research**

Practice: The authors stated that the risk of fractures associated with psychotropic medication should be considered when initiating treatment with these drugs.

Research: The authors stated the need for further prospective studies that control for confounding variables to accurately measure the risk of fracture with psychotropic medications, and the need to evaluate high-risk populations and the risks associated with newer medications.

**Bibliographic details**


**PubMedID**

17253881

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Adult; Aged; Analgesics, Opioid /adverse effects; Anticonvulsants /adverse effects; Antidepressive Agents /adverse
AccessionNumber
12007000943

Date bibliographic record published
30/11/2007

Date abstract record published
30/11/2007

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.